REMARKS

Upon entering the above amendments, claims 1, 6-10, 12-30, 32-43, 48-52, 54-64, 69-73, 75-89 and 90-91 will be pending in this application and are presented for examination. Claims 3, 5, 45, 47, 68 and 96-101 have been withdrawn from consideration by the Examiner. Claims 1, 2, 4, 6-41, 43, 44, 46, 48-67 and 69-95 stand rejected. Claims 2-5, 11, 31, 44-47, 53, 65-68, 74 and 92-101 are now canceled by Applicants without forfeiting any right to pursue canceled subject matter in a subsequent divisional or continuation application. Claims 1, 6-9, 12-13, 22, 42-43, 54-55, 64, 69-72, 75-76 and 90-91 have been amended.

Reconsideration of the application is respectfully requested in view of the above amendments to the claims and the following remarks. For the Examiner's convenience and reference, Applicants' remarks are presented in the order in which the corresponding issues were raised in the Office Action.

Applicants thank the Examiner for noting allowable subject matter in claim 42.

Amendments to the claims find support throughout the specification and original claims as filed. In particular, page 8, lines 1-19 provides support for the nitrogen atoms of the heterocyclyl rings. Additional amendments are intended to focus the scope of the claims around the most preferred compounds, as well as to correct minor typographical errors. Applicants believe no new matter is present in this or any other portion of the present amendment.

I. Rejection under 35 U.S.C. § 112, 1st paragraph

The Examiner has rejected claims 64-67 and 69-95 of the present application under 35 U.S.C. § 112, 1st paragraph as allegedly lacking enablement for any or all TNF-α mediated disorders. To the extent the rejection is applicable to the amended set of claims, Applicants respectfully traverse the rejection.

Applicants respectfully note that claims 92-95 have been canceled, and independent claims 64 and 91 have been amended to inflammatory conditions and cancer. These disease conditions are characterized by being mediated by IKK in the expression of TNF-α

activity. Support for inflammatory conditions being mediated by IKK can be found in the publications forwarded by the Examiner (Shaw *et al.* and Graninger *et al.*) Both of these publications discuss in great detail the role that IKK and TNF-α play in rheumatoid arthritis.

In addition, support for the role of IKK in inflammatory conditions can be found in May *et al. Science* **2000**, *289*, 1550 (Exhibit A):

> Activation of the transcription factor (NF)-κB by proinflammatory stimuli leads to increased expression of genes involved in inflammation. Activation of NF-κB requires the activity of an inhibitor of κB (IκB)-kinase (IKK) complex containing two kinases (IKKα and IKKβ) and the regulatory protein NEMO (NF-κB essential modifier).

Further support can be found in Rossi *et al. Nature* **2000**, *403*, 103 (Exhibit B):

> NF-κB is a critical activator of genes involved in inflammation and immunity. Pro-inflammatory cytokines activate the IκB kinase (IKK) complex that phosphorylates the NF-κB inhibitors, triggering their conjugation with ubiquitin and subsequent degradation.

Moreover, Karin *et al. Seminars in Immunology* **2000**, *12*, 85 (Abstract, Exhibit C) provides additional support for the critical role of IKK in inflammatory diseases:

> There is strong biochemical and genetic evidence that the IKK complex...is the master regulator of NF-κB mediated innate immune and inflammatory responses.

Regarding cancer, Karin *et al.* states in the *Journal of Biological Chemistry* **1999**, *274(39)*, 27339 (Exhibit D), that:

> [E]levated NF-κB and IKK activity may protect numerous types of tumors from apoptosis-inducing therapies (49). Thus, IKK offers a reasonable target for development of new anti-tumor drugs.

Additional evidence for the application of the compounds of the present invention as inhibitors of IKK, and treatment of inflammatory conditions and cancer, can be found in the assay in Example 12. Those compounds that exhibit low IC_{50} values in the prescribed assay, are good inhibitors of IKK activity, and thus, are capable of treating inflammatory conditions and cancer.

Accordingly, Applicants respectfully submit that in view of the amendments to the claims focusing on inflammatory conditions and cancer, that the specification, particularly Example 12, provides sufficient support to enable the claims as amended. As such, Applicants respectfully request that the rejection be withdrawn.

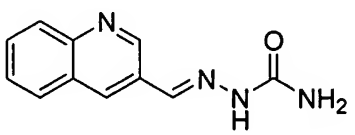
II. Rejection under 35 U.S.C. § 103(a)

The Examiner has further rejected claims 1-2, 4, 6-41, 43-44, 46, 48-67 and 69-95 of the instant application under 35 U.S.C. § 103(a) as allegedly being obvious in view of Wang *et al.* (WO 98/47869). To the extent the rejection is applicable to the amended set of claims, Applicants respectfully traverse the rejection.

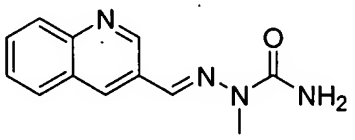
As the Examiner can see, the claims of the present application have been amended to a genus focused around the compounds of claim 42: W is N, X is CH, A is a 6-membered fused aromatic or 1-2 N containing heteroaromatic, and B is a 5- or 6-membered heteroaryl containing at least 1 nitrogen. Neither the schemes nor examples of Wang *et al.*, however, teach or suggest the combination of a pyridyl ring (fused to another aromatic) *directly* linked to another nitrogen containing heteroaryl, with a semicarbazone or thiosemicarbazone ***para*** to the pyridyl nitrogen. The Examiner points to examples 1-28 of Wang *et al.*, and alleges that:

> Wang *et al.* teaches the equivalency of exemplified heterocyclic semicarbazones and thiosemicarbazones bearing a heteroring linked through a X group with those wherein X is a direct bond in the definition of various variable group of X of formula I.

Applicants respectfully note that a conservative calculation of the number of compounds encompassed by Formula I of Wang *et al.* is 21,954,240 (9x10x7x11x11x2x12x12)! Of this large number of compounds possible, only two of the compounds of Wang *et al.* teach a pyridyl fused to another aromatic:



3-quinolinecarboxaldehyde semicarbazone



3-quinolinecarboxaldehyde 2'-methylsemicarbazone

These compounds of Wang *et al.*, however, do **not** have an additional heteroaryl directly linked to the pyridyl ring. Furthermore, the semicarbazone is *meta* to the ring nitrogen, while the present invention teaches the semicarbazone *para* to the ring nitrogen.

As Wang *et al.* fails to teach or suggest a pyridyl ring fused to another aromatic, with an additional heteroaryl directly linked to the pyridyl, and with the semicarbazone *para* to

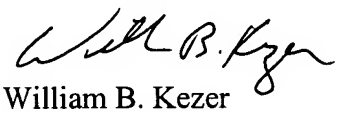
the ring nitrogen, Applicants submit that the claims of the instant application are not obvious in view of Wang *et al.* Accordingly, Applicants respectfully request that the rejection be withdrawn.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 925-472-5000.

Respectfully submitted,



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